

Response Under 37 C.F.R. §1.192
Appellant's Brief
Application No. 10/057,323
Paper Dated: December 2, 2008
Attorney Docket No. CV01489K (4686-045531)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

In re Patent Application of:	:	
Harry R. DAVIS, et al.	:	Examiner: San-Ming R. Hui
	:	
Serial No.: 10/057,323	:	Group Art Unit: 1617
	:	
Filed: January 25, 2002	:	Atty. Docket No.: CV01489K
	:	
For: COMBINATIONS OF PEROXISOME	:	
PROLIFERATOR-ACTIVATED	:	
RECEPTOR (PPAR) ACTIVATOR(S)	:	
AND STEROL ABSORPTION	:	
INHIBITOR(S) AND TREATMENTS	:	
FOR VASCULAR INDICATIONS	:	

MAIL STOP APPEAL BRIEF – PATENTS

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**ON APPEAL FROM THE PRIMARY EXAMINER TO THE
BOARD OF PATENT APPEALS AND INTERFERENCES**

APPELLANT'S BRIEF UNDER 37 C.F.R. § 1.192

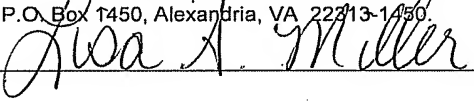
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I

REAL PARTY IN INTEREST

The real party in interest in this Appeal is assignee Schering Corporation, having a principal place of business 2000 Galloping Hill Road, Kenilworth, NJ 07033.

II

RELATED APPEALS AND INTERFERENCES

This application (10/057,323) was previously the subject of an appeal entitled Ex parte Harry R. Davis, Teddy Kosoglou, and Gilles J. Picard, which was assigned Appeal No. 2007-0181. A decision on this appeal was rendered June 28, 2007. A copy of this decision is included in the Related Proceedings Appendix.

III

STATUS OF CLAIMS

Claims 32 and 102-126 are pending in this application. Claims 105, 109 and 113-125 have been withdrawn by the Examiner as being drawn to a non-elected invention.

Claims 32, 102-104, 106-108, 110-112 and 126 (pending) were finally rejected under 35 U.S.C. §103(a) in an Office Action mailed September 26, 2008 ("Final Office Action").

Eleven (11) pending claims (32, 102-104, 106-108, 110-112 and 126) are at issue in this Appeal.

IV

STATUS OF AMENDMENTS

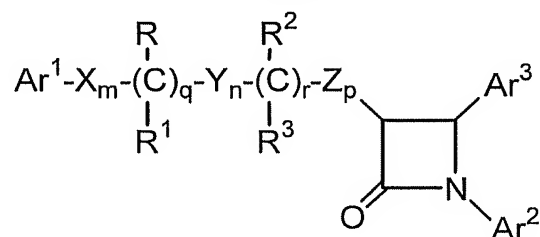
No claims were amended after final rejection. A copy of the claims involved in this Appeal is contained in the Claims Appendix attached hereto.

V

SUMMARY OF CLAIMED SUBJECT MATTER

In one embodiment, set forth in claim 32, Applicants have discovered a composition comprising:

- (a) at least one peroxisome proliferator-activated receptor (PPAR) activator;
- (b) at least one sterol absorption inhibitor represented by Formula (I):



(I)

or isomers thereof, or pharmaceutically acceptable salts, solvates or prodrugs thereof (see original claim 1 for moiety definitions); and

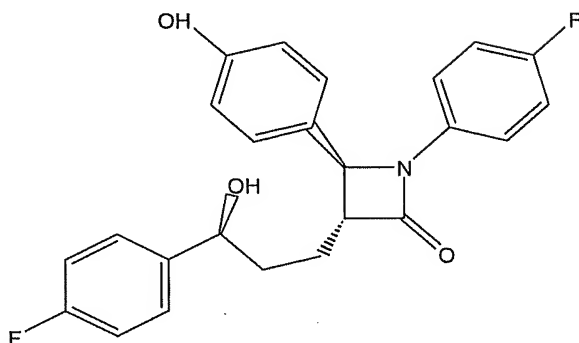
- (c) at least one cardiovascular agent selected from the group consisting of calcium channel blockers, adrenergic blockers, adrenergic stimulants, angiotensin converting enzyme (ACE) inhibitors, antihypertensive, angiotensin II receptor antagonists, anti-anginal agents, coronary vasodilators, diuretics and combinations thereof.

See claim 32; page 3, line 6 – page 4, line 17; and page 76, line 7 – page 77, line 19 of the specification.

In the Office Action of July 2, 2003, Applicants were required to elect a species of peroxisome proliferator-activated receptor (PPAR) activator, sterol absorption inhibitor, and third therapeutic agent.

Applicants provisionally elected with traverse fenofibrate as the PPAR activator. See Response to Restriction Requirement and Election of Species of August 1, 2003 at page 2, lines 8-9.

Applicants provisionally elected with traverse ezetimibe as the sterol absorption inhibitor, represented by Formula (II) below:



(II).

Ezetimibe is the active ingredient in ZETIA™ (ezetimibe) pharmaceutical formulation and VYTORIN™ (ezetimibe/simvastatin) pharmaceutical formulation, both of which are commercially available from MSP (Merck Schering-Plough) Pharmaceuticals, Inc. See Response to Restriction Requirement and Election of Species of August 1, 2003 at page 2, lines 12-13.

In the same Response, Applicants provisionally elected niacin as the third therapeutic agent. See Response to Restriction Requirement and Election of Species of August 1, 2003 at page 2, lines 15-16.

The combination of ezetimibe, fenofibrate, and niacin was finally rejected by the Examiner in a Final Office Action mailed September 20, 2004.

On appeal from this final rejection, the Board reversed the Examiner's finding that the combination of ezetimibe, fenofibrate, and niacin was obvious. See Ex Parte Harry R. Davis et al., Appeal No. 2007-0181, Decided June 28, 2007. After the decision, claim 32 was rewritten in independent form.

On remand to the Examiner, the Examiner indicated that the next specie of the third therapeutic agent, ACE inhibitor, and specifically captopril, would be examined in connection with claim 32. See Office Action of October 22, 2007 at page 2.

The claimed compositions and combinations can be useful for treating vascular conditions, diabetes, obesity and/or lowering concentration of a sterol in plasma in a mammal (page 22, lines 8-15 of the specification).

GROUND OF REJECTION TO BE REVIEWED ON APPEAL

- I. Has a Prima Facie Case of Obviousness Under 35 U.S.C. § 103(a) Over US 5,846,966 ("Rosenblum et al."), The Medical Letter on Drugs and Therapeutics (1998) 40:1030: 68-69 ("Medical Letter") and EP 0 457 514 ("Bergey et al.") Been Established?

VII

ARGUMENT

- I. The Required Prima Facie Case of Obviousness Under 35 U.S.C. § 103(a) Over US 5,846,966 ("Rosenblum et al."), The Medical Letter on Drugs and Therapeutics (1998) 40:1030: 68-69 ("Medical Letter") and EP 0 457 514 ("Bergey et al.") has Failed to be Established.

A. The Rejection

Claims 32, 102-104, 106-108, 110-112 and 126 have been rejected under 35 U.S.C. §103(a) as obvious over US 5,846,966 ("Rosenblum et al."), The Medical Letter on Drugs and Therapeutics (1998) 40:1030: 68-69 ("Medical Letter") and EP 0 457 514 ("Bergey et al.").

The reasons for rejection are set forth in the Final Office Action, summarized as follows:

Rosenblum et al. allegedly teaches that the elected compound of Formula II, ezetimibe, is useful for reducing cholesterol and the risk of atherosclerosis (Final Office Action at page 3). Medical Letter allegedly teaches fenofibrate as useful in reducing serum cholesterol (Final Office Action at page 3). Bergey et al. allegedly teaches that captopril is useful in significantly reducing serum cholesterol in hypercholesterolemic patients and is beneficial as an anti-atherosclerosis agent to slow or regress the progress of atherosclerosis. (Final Office Action at page 3). Bergey et al. also allegedly teaches the combination of captopril with an additional cholesterol lowering agent such as HMG-CoA reductase inhibitors. (Final Office Action at page 3).

The Office Action acknowledges that the references do not expressly teach the claimed composition comprising ezetimibe, fenofibrate and captopril together (Final Office Action at page 4).

It is alleged that it would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate ezetimibe, fenofibrate and captopril together in a single composition since the cited art teaches that ezetimibe, fenofibrate and captopril are useful in reducing cholesterol and the risk of atherosclerosis individually, citing In re Kerkhoven, 626 F.2d 846, 205 U.S.P.Q. 1069 (CCPA 1980). (Final Office Action at page 4). Furthermore, the Office Action alleges that Bergey et al. teaches that captopril is known to be useful in combination with cholesterol lowering agents and, therefore, one skilled in the art would have been motivated to incorporate the claimed compounds together in a single composition for reducing cholesterol and the risk of atherosclerosis. (Final Office Action at page 4).

B. The Prior Art

Rosenblum et al. disclose the compound of Formula II (Col. 32, Ex. 6). Rosenblum et al. disclose starch-based pharmaceutical compositions including compounds of Formula I of Rosenblum et al. (Col. 39-40, Ex. A and B). Rosenblum et al. teach that the active compounds therein can be combined with HMG CoA reductase inhibitors, such as simvastatin (Col. 6, lines 37-50). Rosenblum et al. also disclose that the active compounds are useful for reducing cholesterol and the risk of atherosclerosis (claims).

Medical Letter teaches fenofibrate as useful in reducing VLDL cholesterol and triglycerides (Medical Letter at page 68).

Bergey et al. teaches a method for slowing the progression of atherosclerosis in hypertensive or normotensive patients and reducing or eliminating atherosclerotic lesions by administering a combination of a cholesterol lowering drug such as pravastatin and an ACE inhibitor such as captopril or zofenopril. (Abstract).

C. The Required *Prima Facie* Case of Obviousness Under
35 U.S.C. § 103 Has Not Been Established

When making a rejection under 35 U.S.C. § 103, the Examiner has the burden of establishing a prima facie case of obviousness. In re Fritch, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992). The Examiner can satisfy this burden only by showing an objective teaching in the prior art, or knowledge generally available to one of ordinary skill in the art, which would lead an individual to combine the relevant teachings of the references [and/or the knowledge] in the manner suggested by the Examiner. KSR Int'l Co. v. Teleflex Inc., 127 S.Ct. 1727, 82 U.S.P.Q.2d 1385 (2007).

In KSR Int'l, the Court acknowledged the importance of identifying a reason that would have prompted a person of ordinary skill in the art to combine the elements in the way the claimed invention does. KSR Int'l, 127 S.Ct. at 1731, 82 U.S.P.Q.2d at 1396. The KSR Int'l decision repeatedly emphasizes the importance that the result obtained by a particular combination is predictable to one of ordinary skill in the art. KSR Int'l, 127 S.Ct. at 1731 and 1739-1742, 82 U.S.P.Q. at 1389 and 1395-1397. Thus, the mere fact that the prior art could be modified does not make the modification obvious unless there is a rationale justifying the modification that is gleaned from the prior art or the knowledge of the ordinary artisan.

Claim 32 recites a composition comprising a sterol absorption inhibitor of Formula I shown above or isomers, prodrugs, or pharmaceutically acceptable salts or solvates thereof; at least one PPAR activator; and at least one cardiovascular agent selected from the group consisting of calcium channel blockers, adrenergic blockers, adrenergic stimulants, angiotensin converting enzyme (ACE) inhibitors, antihypertensive, angiotensin II receptor antagonists, anti-anginal agents, coronary vasodilators, diuretics and combinations thereof.

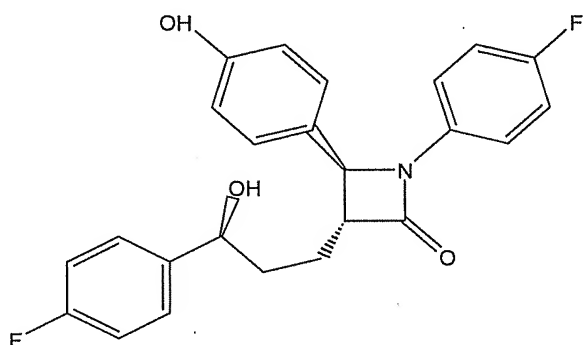
Claim 102 depends from claim 32 and recites that the at least one PPAR activator is a fibric acid derivative.

Claim 103 depends from claim 102 and recites that the fibric acid derivative is selected from, inter alia, fenofibrate.

Claim 104 depends from claim 103 and recites that the fibric acid derivative is fenofibrate.

Claim 106 depends from claim 32 and recites that the amount of PPAR activator administered to a mammal ranges from about 50 to about 3000 mg/day.

Claim 107 depends from claim 32 and recites that the sterol absorption inhibitor is represented by Formula (II) below, or a prodrug or pharmaceutically acceptable salts or solvates thereof:



(II)

Claim 108 depends from claim 107 and recites that the fibric acid derivative comprises fenofibrate.

Claim 110 depends from claim 32 and recites that the at least one sterol absorption inhibitor is administered to a mammal in an amount ranging from about 0.1 to about 1000 mg/day.

Claim 111 depends from claim 32 and recites that the cardiovascular agent is an angiotensin converting enzyme (ACE) inhibitor.

Claim 112 depends from claim 111 and recites that the cardiovascular agent is captopril.

Claim 126 recites a pharmaceutical composition for the treatment of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal using the composition of claim 32 and a carrier.

It is respectfully submitted that the combination of the references cited as rendering the claimed invention obvious is improper because there is no

rationale for making a triple combination treatment of the claimed components of a sterol absorption inhibitor (such as that of Formula (I) (e.g., ezetimibe)), a PPAR activator (such as fenofibrate) and a cardiovascular agent (such as the ACE inhibitor captopril) as defined in claim 32.

As admitted in the Office Action, "[t]he references do not expressly teach a composition containing fenofibrate, ezetimibe, and captopril together." (Office Action at page 4). It is then suggested that one skilled in the art would find it obvious to make this triple combination since the prior art teaches each of these components as useful in reducing cholesterol and the risk of atherosclerosis individually. However, the rationale presented by the Examiner is the result of an improper hindsight reconstruction of the claims. While each of the components of Applicants' triple combination are, individually, taught in the art, the selection and incorporation of these components into a single composition would not be obvious to the ordinary artisan. "A patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the art." KSR Int'l 127 S.Ct. at 1741, 82 U.S.P.Q.2d at 1396. "This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." Id.

Here, the Examiner has culled individual compounds from three prior art references to form the claimed triple combination composition. It is alleged that this combination is obvious because, in each of the prior art references, the compounds were used in compositions for lowering serum cholesterol levels. However, this rationale overlooks certain aspects of the prior art that would suggest to one skilled in the art that no such combination is warranted. The prior art must be evaluated based on what it, as a whole, teaches to one of ordinary skill in the art. In re McLaughlin, 443 F.2d 1392, 170 U.S.P.Q. 209 (C.C.P.A. 1971).

Rosenblum et al. is directed to a composition of ezetimibe and a statin. As disclosed in the Medical Letter Clinical Study section at page 68, fenofibrate is not as effective as statins in lowering LDL cholesterol, a major

risk factor in atherogenesis. Since statins are more effective in lowering LDL cholesterol, there is no reason to combine a PPAR activator such as fenofibrate with the ezetimibe compound disclosed in Rosenblum et al.

There is also no reason in the cited art to combine an ACE inhibitor (e.g. captopril) with ezetimibe. Bergey et al. asserts that captopril was found to significantly reduce serum cholesterol and increase HDL. (Bergey et al., page 2, lines 17-19). Bergey et al. also asserts that there is no evidence that these therapeutic effects result from inhibition of the cholesterol synthetic pathway, and thus the therapeutic mechanism for ACE inhibitors is different from that of HMG CoA reductase inhibitors such as statins. (Bergey et al., page 2, lines 19-22). Based on this information, Bergey et al. propose a combination of a HMG CoA reductase inhibitor and an ACE inhibitor. (Bergey et al., page 8, lines 18-22). According to Bergey et al., combination therapy of drugs known to have separate mechanisms of action is preferred over monotherapy since co-administration can produce a maximum therapeutic effect which is greater than can be achieved when either drug is given alone. (Bergey et al., page 8, lines 34-43). Thus, according to Bergey et al., ACE inhibitors can be combined with cholesterol lowering drugs that inhibit cholesterol through a mechanism of action unique from the mechanism of action of ACE inhibitors to create a composition for treating atherosclerosis.

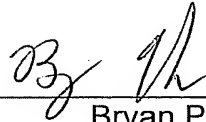
Here, the mechanism of action of ezetimibe was unknown at the time of Applicants' invention, as evidenced by a recent article from Expert Opinion on Pharmacotherapy attached as Exhibit A (Submitted in Applicants' Request for Reconsideration dated July 8, 2008). In this article, published in 2007, the author states that "[t]he exact mechanism of action [of ezetimibe] is not yet fully elucidated." (Farnier, Expert Opin. Pharmacother. 2007, 8(9), page 1346). Thus, regardless of whether Bergey et al. teaches the usefulness of captopril alone in reducing serum cholesterol levels, one skilled in the art having read Bergey et al. would not find it obvious to combine ezetimibe and captopril, much less make the triple combination of ezetimibe, captopril and fenofibrate, absent an understanding of the mechanism of action of ezetimibe.

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Therefore, the prima facie case of obviousness based upon Rosenblum et al., Medical Letter and Bergey et al. has not been established and the rejection of claims 32, 102-104, 106-108, 110-112 and 126 should be reconsidered and withdrawn.

Respectfully submitted,

Date: December 2, 2008

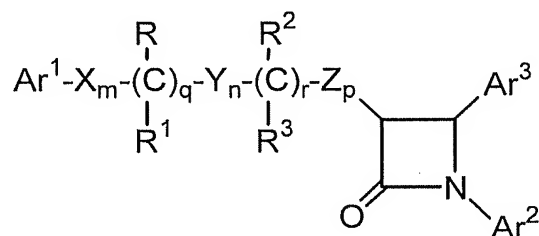


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CLAIMS APPENDIX

32. A composition comprising:

- (a) at least one peroxisome proliferator-activated receptor activator;
- (b) at least one sterol absorption inhibitor represented by Formula (I):



(I)

or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (I) or of the isomers thereof, or prodrugs of the compounds of Formula (I) or of the isomers, salts or solvates thereof, wherein in Formula (I) above:

Ar^1 and Ar^2 are independently selected from the group consisting of aryl and R^4 -substituted aryl;

Ar^3 is aryl or R^5 -substituted aryl;

X, Y and Z are independently selected from the group consisting of $\text{-CH}_2\text{-}$, -CH(lower alkyl)- and $\text{-C(dilower alkyl)-}$;

R and R^2 are independently selected from the group consisting of -OR^6 , -O(CO)R^6 , -O(CO)OR^9 and $\text{-O(CO)NR}^6\text{R}^7$;

R^1 and R^3 are independently selected from the group consisting of hydrogen, lower alkyl and aryl;

q is 0 or 1;

r is 0 or 1;

m, n and p are independently selected from 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1, 2, 3, 4, 5 or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or 5;

R⁴ is 1-5 substituents independently selected from the group consisting of lower alkyl, -OR⁶, -O(CO)R⁶, -O(CO)OR⁹, -O(CH₂)₁₋₅OR⁶, -O(CO)NR⁶R⁷, -NR⁶R⁷, -NR⁶(CO)R⁷, -NR⁶(CO)OR⁹, -NR⁶(CO)NR⁷R⁸, -NR⁶SO₂R⁹, -COOR⁶, -CONR⁶R⁷, -COR⁶, -SO₂NR⁶R⁷, S(O)₀₋₂R⁹, -O(CH₂)₁₋₁₀-COOR⁶, -O(CH₂)₁₋₁₀CONR⁶R⁷, -(lower alkylene)COOR⁶, -CH=CH-COOR⁶, -CF₃, -CN, -NO₂ and halogen;

R⁵ is 1-5 substituents independently selected from the group consisting of -OR⁶, -O(CO)R⁶, -O(CO)OR⁹, -O(CH₂)₁₋₅OR⁶, -O(CO)NR⁶R⁷, -NR⁶R⁷, -NR⁶(CO)R⁷, -NR⁶(CO)OR⁹, -NR⁶(CO)NR⁷R⁸, -NR⁶SO₂R⁹, -COOR⁶, -CONR⁶R⁷, -COR⁶, -SO₂NR⁶R⁷, S(O)₀₋₂R⁹, -O(CH₂)₁₋₁₀-COOR⁶, -O(CH₂)₁₋₁₀CONR⁶R⁷, -(lower alkylene)COOR⁶ and -CH=CH-COOR⁶;

R⁶, R⁷ and R⁸ are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

R⁹ is lower alkyl, aryl or aryl-substituted lower alkyl; and

(c) at least one cardiovascular agent selected from the group consisting of calcium channel blockers, adrenergic blockers, adrenergic stimulants, angiotensin converting enzyme (ACE) inhibitors, antihypertensive, angiotensin II receptor antagonists, anti-anginal agents, coronary vasodilators, diuretics and combinations thereof.

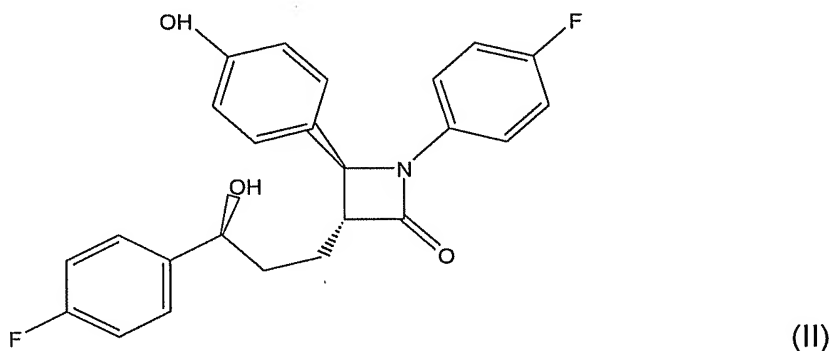
102. The composition according to claim 32, wherein the at least one peroxisome proliferator-activated receptor activator is a fibric acid derivative.

103. The composition according to claim 102, wherein the fibric acid derivative is selected from the group consisting of fenofibrate, clofibrate, gemfibrozil, ciprofibrate, bezafibrate, clinofibrate, binifibrate, lifibrol and mixtures thereof.

104. The composition according to claim 103, wherein the fibric acid derivative comprises fenofibrate.

106. The composition according to claim 32, wherein the at least one peroxisome proliferator-activated receptor activator is administered to a mammal in an amount ranging from about 50 to about 3000 milligrams of peroxisome proliferator-activated receptor activator per day.

107. The composition according to claim 32, wherein the sterol absorption inhibitor is represented by Formula (II) below:



or pharmaceutically acceptable salt or solvate thereof, or prodrug of the compound of Formula (II) or of the salt or solvate thereof.

108. The composition according to claim 107, wherein the fibric acid derivative comprises fenofibrate.

110. The composition according to claim 32, wherein the at least one sterol absorption inhibitor is administered to a mammal in an amount ranging from about 0.1 to about 1000 milligrams of sterol absorption inhibitor per day.

111. The composition according to claim 32, wherein the cardiovascular agent is an angiotensin converting enzyme (ACE) inhibitor.

112. The composition according to claim 111, wherein the cardiovascular agent is captopril.

126. A pharmaceutical composition for the treatment of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising a therapeutically effective amount of the composition of claim 32 and a pharmaceutically acceptable carrier.

EVIDENCE APPENDIX

Exhibit A: Farnier, "Ezetimibe plus fenofibrate: a new combination therapy for the management of mixed hyperlipidaemia?", Expert Opin. Pharmacother. 2007, 8(9), pages 1345-52. (Submitted with Applicants' Request for Reconsideration dated July 8, 2008.)

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RELATED PROCEEDINGS APPENDIX

Exhibit B: Ex parte Harry R. Davis, Teddy Kosoglou, and Gilles J. Picard, Appeal 2007-0181, Application No. 10/057,323, Decided June 28, 2007.